(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 May 2001 (10.05.2001)

PCT

(10) International Publication Number
WO 01/32828 A2

(51) International Patent Classification[7]: C12M 1/34, 1/12

(21) International Application Number: PCT/US00/29543

(22) International Filing Date: 27 October 2000 (27.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/162,234	29 October 1999 (29.10.1999)	US
60/178,746	28 January 2000 (28.01.2000)	US
60/216,467	6 July 2000 (06.07.2000)	US

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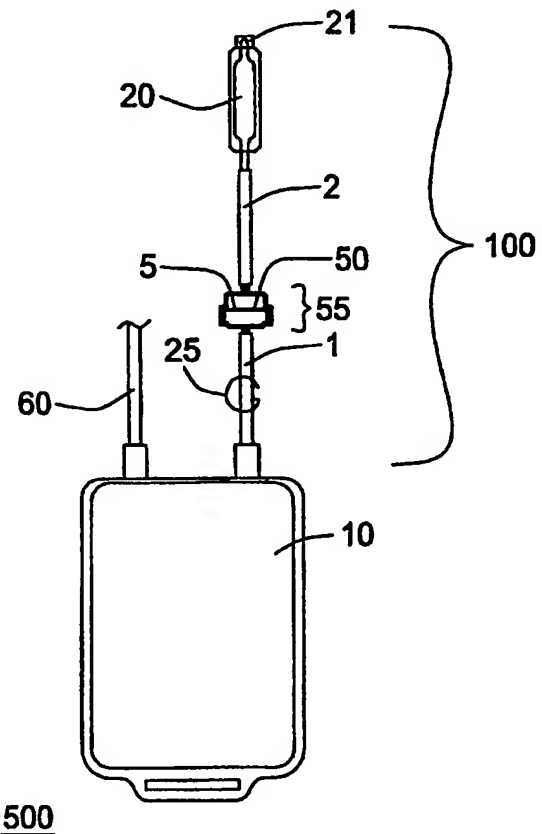
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European

[Continued on next page]

(54) Title: BIOLOGICAL FLUID PROCESSING



(57) Abstract: A system including a container (10) for biological fluid, and a processing arrangement (100) comprising an analysis chamber (20) for a test portion of the biological fluid, and a filter (50) allowing the passage of microorganism-containing biological fluid from the container to the chamber, is disclosed.

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patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

BIOLOGICAL FLUID PROCESSING

This application claims the benefit of U.S. Provisional Application Nos. 60/162,234, filed October 29, 1999; 60/178,746, filed January 28, 2000; and 60/216,467, filed July 6, 2000, each of which is incorporated by reference.

TECHNICAL FIELD

This invention relates to analyzing a biological fluid such as blood and blood components, e.g., to determine the presence of material, preferably microorganisms such as bacteria, in a portion of the fluid.

BACKGROUND OF THE INVENTION

Blood is conventionally processed, e.g., separated into components, to provide a variety of valuable products such as transfusion products. Blood components or products such as buffy coat and platelets may be pooled during processing, e.g., 4-6 units of platelet concentrate can be pooled before administration as a transfusion product. Additionally, blood components processed in a closed system (e.g., without exposing the components to the outside environment) can be stored before administration. For example, red blood cells can be stored for several weeks, and platelets can be stored for several days (e.g., 5 days according to current U.S. practice).

Stored and/or non-stored components typically include undesirable material such as bacteria. Bacteria can contaminate the blood or blood component during blood collection (including blood sampling) and/or storage. One source of bacterial contamination may be the blood donor's skin, which may contain one or more varieties of bacteria, e.g., gram positive bacteria such as Staphylococcus epidermidis and Staphylococcus aureus, and/or gram negative bacteria such as Serratia marcescens and Serratia liquefaciens. Other bacterial contaminants include, for example, coagulase negative staphylococci, and Yersinia enterocolitica.

Since swabbing the donor's skin (e.g., with alcohol) prior to venipuncture may be inadequate to assure sterility, the bacteria may pass into the blood collection container,

and the bacteria may reproduce while the blood or blood component is stored. Additionally, phlebotomy needles may cut a disc of skin when the phlebotomy needle is inserted into the donor, allowing the bacteria-containing skin plug to pass with the blood into the blood collection container.

Other sources of contamination include the donor's blood, the environment (including the air, and the equipment in the environment), and the phlebotomist. Contamination can occur while the unit of blood is being donated and/or while samples of blood are being obtained.

Since some blood components (e.g., platelets) are typically stored at ambient temperatures, the problem of contamination may be magnified, as most bacteria reproduce more rapidly at ambient temperatures.

Contaminated blood products, especially bacterially contaminated blood products, pose a potential health risk to those who come into contact with, or receive, these products. For example, the administration of transfusion products with bacterial contamination can have adverse affects on the recipient, and the administration of platelets with massive levels of bacterial contamination is implicated in about 150 cases of severe morbidity or death each year in the U.S.

Some bacterial detection techniques include opening the container of collected blood, obtaining a sample of the blood, transferring the sample to a container including a growth medium, and incubating the bacteria. The bacteria are subsequently detected, e.g., by changes in pH.

However, these techniques are labor- and time-intensive and may require expensive equipment. Some of the techniques may provide inaccurate results. Additionally, the techniques may introduce contamination from the environment into the samples.

The present invention provides for ameliorating at least some of the disadvantages of the prior art. These and other advantages of the present invention will be apparent from the description as set forth below.

SUMMARY OF THE INVENTION

In accordance with an embodiment of the invention, a system is provided comprising a first container suitable for containing a biological fluid, and a processing arrangement comprising a biological fluid analysis chamber suitable for receiving a microbe- and plasma-containing portion of biological fluid from the first container and a filter interposed between the first container and the analysis chamber, wherein the filter allows a microbe- and plasma-containing portion of biological fluid to pass from the first container to the analysis chamber, while reducing the passage of at least one of platelets, red blood cells and white blood cells therethrough, and the system is disposed to allow the detection of microbes in the analysis chamber. In an embodiment, the first container is suitable for holding a plurality of units of biological fluid (e.g., pooled platelet concentrate). In some embodiments, the analysis chamber can be detached from other components of the system before the microbes are detected.

The system is disposed to allow microbes in the biological fluid passing through the filter to be detected, preferably by detecting an indicator of microbe metabolism in the analysis chamber. In a preferred embodiment, the system is disposed to allow the early detection of clinically significant levels of bacteria in the analysis chamber.

A method according to an embodiment of the instant invention provides a filtered, microbe-containing sample of biological fluid in a biological fluid analysis chamber, wherein microbes in the filtered sample are subsequently detected. In a preferred embodiment, the filtered, microbe-containing sample comprises a plasma-rich, bacteria-containing, platelet-reduced fluid. In some embodiments, the filtered sample comprises a red blood cell and/or white blood cell-depleted plasma-rich fluid.

Systems and methods according to the present invention are especially suitable for use by transfusion services, blood centers and/or blood bank personnel.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is an embodiment of a system according to the present invention, including a container, and a processing arrangement including a filter and an analysis chamber, wherein the analysis chamber includes a port (e.g., allowing communication

with a probe device).

Figure 2 is another embodiment of a system according to the present invention, including a container, and a processing arrangement including a filter and an analysis chamber.

Figure 3 is another embodiment of a system according to the present invention, including a plurality of containers, and a processing arrangement including a filter and an analysis chamber.

SPECIFIC DESCRIPTION OF THE INVENTION

In accordance with an embodiment of the invention, a biological fluid processing system comprises a first container suitable for holding a biological fluid, the container having an internal volume for receiving the biological fluid, and a processing arrangement comprising an analysis chamber, suitable for receiving a plasma-containing portion of biological fluid passed from the internal volume of the container and a filter interposed between, and in fluid communication with, the first container and the analysis chamber, the filter comprising at least one filter element including at least one porous medium, wherein the filter allows the passage of microbes and plasma from the first container to the analysis chamber, and reduces the passage of platelets from the first container to the analysis chamber.

A biological fluid processing system provided by another embodiment of the invention comprises a first flexible container suitable for holding a biological fluid, the container having an internal volume for receiving the biological fluid, and a processing arrangement comprising a biological fluid analysis chamber, adapted for receiving a microbe- and plasma-containing portion of biological fluid passed from the internal volume of the first flexible container and a filter interposed between, and in fluid communication with, the first flexible container and the biological fluid analysis chamber, the filter comprising at least one filter element including at least one porous medium, wherein the filter allows the passage of microbes and plasma from the first flexible container to the analysis chamber, and reduces the passage of white blood cells from the first flexible container to the analysis chamber, wherein the system is arranged

to allow microbes in the biological fluid passing through the filter to be detected, e.g., in the analysis chamber.

In accordance with yet another embodiment, a microbe detection system is provided comprising a first container suitable for holding a biological fluid to be analyzed for the presence of microbes, the container having an internal volume for receiving the biological fluid; a microbe detection chamber, adapted for receiving a microbe-containing portion of the biological fluid passed from the internal volume of the first flexible container; a filter interposed between, and in fluid communication with, the first flexible container and the microbe detection chamber, the filter allowing a portion of the microbes in the biological fluid to pass from the first flexible container into the detection chamber, wherein the detection system is arranged to allow microbes to be detected in the microbe detection chamber.

Another embodiment of a biological fluid processing system according to the invention comprises a first container suitable for holding a biological fluid, the container having an internal volume for receiving the biological fluid, and a filter in fluid communication with the first container, the filter comprising at least one filter element including at least one porous medium, the filter including an analysis chamber, suitable for receiving a plasma-containing portion of biological fluid passed from the internal volume of the container, wherein the filter allows the passage of microbes and plasma from the first container to the analysis chamber, and reduces the passage of platelets from the first container to the analysis chamber.

In some embodiments of the system, the filter reduces the passage of at least one of platelets, white blood cells and red blood cells (more preferably, reducing the passage of platelets and white blood cells), from the first container to the analysis chamber.

In one embodiment of the system, the first container is suitable for holding two or more units of blood components, e.g., pooled or combined platelets, for example, multiple units of buffy coat or platelet concentrate. Illustratively, the first container can be suitable for holding four or more combined units of platelet concentrate (PC).

Embodiments of the system, that can comprise a microbe detection system, can include a detachable analysis chamber. For example, a conduit allowing fluid

communication between the first container and the analysis chamber can be cut (preferably by heat-sealing to maintain the sterility of the contents of the analysis chamber and the first container) after the fluid has been passed therethrough, and the microbes can be subsequently detected. Alternatively, or additionally, the system can include an analysis system that is connected (e.g., to the first container) by a tether, preferably a flexible tether such as a plastic cord or cable. Illustratively, the conduit described above can be cut and sealed, and the separate tether keeps the analysis chamber associated with the first container, e.g., until the microbe analysis is completed.

The present invention also provides a biological fluid analysis device, wherein one embodiment of the device comprises a filter comprising a filter element that allows the passage of plasma- and bacteria-containing biological fluid therethrough, while preventing the passage of blood cells therethrough; and a biological fluid analysis chamber downstream of the filter, wherein the chamber is disposed to receive the fluid passing through the filter, and all fluid passing into the chamber first passes through the filter, the chamber comprising a flexible container.

In accordance with the invention, methods for processing a biological fluid are also provided. For example, in accordance with one embodiment of a method, a biological fluid is passed from a first container through a filter to provide a filtered, microbe-containing portion of biological fluid in an analysis chamber, and microbes present in the filtered portion are subsequently detected. In one preferred embodiment, the method includes passing a biological fluid through a filter to provide a plasma-rich, bacteria-containing, platelet-depleted fluid in the analysis chamber.

Another embodiment of the invention provides a method for processing a platelet-containing biological fluid comprising obtaining a platelet- and plasma-containing biological fluid in a first container (wherein the biological fluid possibly includes microbes), passing a portion of the fluid from the first container into a processing arrangement comprising a filter including at least one filter element including at least one porous medium, wherein the filter allows the passage of microbe- and plasma-containing fluid therethrough and reduces the passage of platelets therethrough, the processing arrangement also including an analysis chamber downstream of the filter

element; receiving a filtered plasma-containing fluid in the analysis chamber; and determining whether microbes are present in the filtered plasma-containing fluid.

In some embodiments of a method according to the invention, two or more units of a biological fluid (e.g., from the same donor, or from different donors) to be analyzed for the presence of microorganisms are pooled or combined, and the biological fluid passed through the filter according to the embodiments described above includes a pooled or combined fluid. For example, four or more units of platelet-containing fluid, e.g., platelet concentrate (PC), can be combined, and a portion of the combined PC is passed through the filter to provide a filtered plasma-containing fluid in the analysis chamber, preferably to provide a plasma-rich, bacteria-containing, platelet- and white blood cell-depleted fluid in the analysis chamber. A variety of techniques, protocols, devices and systems for pooling or combining units are suitable for carrying out the invention and known in the art.

Since microorganisms (especially bacteria) can be detected in accordance with the invention, embodiments of the present invention can be suitable for providing blood components that can be stored for longer periods than are currently allowed by the regulations in various countries. For example, due, at least in part, to fears that platelet concentrate (PC) can be contaminated with bacteria, current U.S. practice requires that individual units of PC be utilized within 5 days, and pooled PC be utilized within 8 hours of pooling. However, since embodiments of the invention allow the detection of contaminated PC, pooled and unpooled PC can be monitored, and if determined to be uncontaminated, can be used after the 5 day/8 hour limits that are currently required. Illustratively, individual units of PC or pooled PC can be transfused after, for example, 7 days of storage.

As used herein, a biological fluid includes any treated or untreated fluid associated with living organisms, including, but not limited to saliva, lymph, cerebrospinal fluid, ascites fluid, and urine, particularly blood, including whole blood, warm or cold blood, and stored or fresh blood; treated blood, such as blood diluted with at least one physiological solution, including but not limited to saline, nutrient, and/or anticoagulant solutions; blood components, such as platelet concentrate (PC), platelet-rich plasma

(PRP), platelet-poor plasma (PPP), platelet-free plasma, plasma, components obtained from plasma, packed red cells (PRC), transition zone material or buffy coat (BC); blood products derived from blood or a blood component or derived from bone marrow; red cells separated from plasma and resuspended in a physiological fluid or a cryoprotective fluid; and platelets separated from plasma and resuspended in a physiological fluid or a cryoprotective fluid.

A "unit" is the quantity of biological fluid from a donor or derived from one unit of whole blood. It may also refer to the quantity drawn during a single donation. Typically, the volume of a unit varies, the amount differing from patient to patient and from donation to donation. Multiple units of some blood components, particularly platelets and buffy coat, may be pooled or combined, typically by combining four or more units.

Each of the components of the invention will now be described in more detail below, wherein like components have like reference numbers.

Figures 1 and 2 illustrate embodiments of a system 500 according to the invention, including at least one container 10, in fluid communication with a processing arrangement 100 comprising a filter 50 (comprising at least one filter element 5 comprising at least one porous medium) and an analysis chamber 20, wherein the filter 50 is interposed between the analysis chamber 20 and the container 10. In the illustrated embodiments, the filter 50 is disposed in a housing to provide a filter device 55, and processing arrangement 100 includes at least two conduits 1, 2, and at least one flow control device 25. The embodiment illustrated in Figure 1 also includes a port 21, e.g., allowing access to the interior of analysis chamber 20.

Figure 3 illustrates another embodiment of a system according to the invention, including a multiple bag set 1000 (such as a multiple blood bag set) comprising containers 11, 12, and 13 in communication with the system 500 comprising a container 10 and a processing arrangement 100 including a filter 50 and an analysis chamber 20. The illustrated set also includes a plurality of filter devices 200 and 201, preferably leukocyte depletion filter devices, a plurality of conduits 60-66, and a connector 40.

In accordance with the invention, the filter 50 comprises at least one filter

element 5 comprising at least one porous medium, wherein the filter allows the passage therethrough of a microbe-containing portion of a biological fluid (if microbes are present in the biological fluid in container 10), while being capable of reducing the passage therethrough of white blood cells. Preferably, the filter 50 reduces the passage therethrough of white blood cells and platelets. In some embodiments, the filter reduces the passage therethrough of red blood cells.

The filter can allow a variety of microbes (microorganisms) to pass therethrough (the terms "microbes" and "microorganisms" are used interchangeably). In a preferred embodiment, the filter allows bacteria to pass therethrough. The filter can allow gram-positive and gram-negative bacteria to pass therethrough. Illustratively, the filter can allow the passage of one or more of the following bacteria: Staphylococcus epidermidis, Staphylococcus aureus, Serratia marcescens, Serratia liquefaciens, Yersinia enterocolitica, Klebsiella pneumoniae, Klebsiella oxytoca, Escherichia coli, Enterobacter cloacae, Enterobacter aerogenes, Pseudomonas aeruginoisa, Salmonella spp., Bacillus spp., such as Bacillus cereus, Group B streptococcus, and coagulase negative staphylococci.

The filter allows sufficient microbes to pass through the filter and to be detected within a suitable amount of time. Typically, as the microbe-containing fluid is passed through the filter, the filter allows at least about 25%, in some embodiments, at least about 50%, or a higher percentage (in some embodiments, about 60% or more), of the microbe(s) of interest to pass therethrough. However, the filter does not necessarily allow the passage of substantially all of the microbes through the filter. For example, the filter can prevent the passage of some of the microbes and/or prevent the passage of some amount of the microbes. Illustratively, as a microbe- and plasma-containing biological fluid is passed from the container 10 to the analysis chamber 20, the filter can remove a level of the microbes from the portion of the biological fluid. Nevertheless, while the level of microbes can be reduced during filtration, sufficient microbes pass through the filter to be detected, more typically, to be detected after a period allowing for microbe growth.

In some embodiments, at least one filter element 5 comprises a membrane, that

can be supported or unsupported. Typically, at least one filter element 5 comprises a fibrous porous medium, preferably a non-woven medium, more preferably a fibrous leukocyte depletion medium, even more preferably a fibrous synthetic polymeric leukocyte depletion medium comprising melt-blown fibers.

A variety of materials can be used, including synthetic polymeric materials, to produce the porous media of the filter elements according to the invention. Suitable synthetic polymeric materials include, for example, polybutylene terephthalate (PBT), polyethylene, polyethylene terephthalate (PET), polypropylene, polymethylpentene, polyvinylidene fluoride, polysulfone, polyethersulfone, nylon 6, nylon 66, nylon 6T, nylon 612, nylon 11, and nylon 6 copolymers.

Suitable media prepared from melt-blown fibers include, but are not limited to, those prepared as disclosed in, for example, U.S. Patent Nos. 4,880,548; 4,925,572, 5,152,905, 5,443,743, 5,472,621, 5,582,907, and 5,670,060, as well as International Publication Nos. WO 91/04088 and WO 93/04763. The filter (and the filter element), which can comprise a preform, can include a plurality of layers and/or media.

In some embodiments, the filter includes a plurality of filter elements and/or a composite filter element, e.g., the filter can include at least two fibrous media, at least one fibrous medium and at least one membrane, or at least two membranes.

The filter element(s) 5 can be treated for increased efficiency in processing a biological fluid. For example, the element may be modified, e.g., surface modified, to affect the critical wetting surface tension (CWST). Typically, an element according to embodiments of the invention, that can comprise, for example, a leukocyte depletion medium, has a CWST of greater than about 53 dynes/cm (about 0.53 erg/mm^2), more typically greater than about 58 dynes/cm (about 0.58 erg/mm^2), and can have a CWST of about 66 dynes/cm (about 0.66 erg/mm^2) or more. In some embodiments, the CWST is 75 dynes (about 0.75 erg/mm^2) or more. In some embodiments, the element may have a CWST in the range from about 62 dynes/cm to about 115 dynes/cm (about 0.62 erg/mm^2 to about 1.62 erg/mm^2), e.g., in the range of about 80 to about 100 dynes/cm (about 0.80 to about 1.00 erg/mm^2). In some embodiments, the element has a CWST of about 85 dynes/cm (0.85 erg/mm^2), or greater, e.g., in the range from about 90 to about 105

dynes/cm (about .90 to about 1.05 erg/mm^2), or in the range from about 85 dynes/cm to about 98 dynes/cm (about .85 to .98 erg/mm^2).

Surface characteristics of the element can be modified (e.g., to affect the CWST, to provide a low affinity for amide-group containing materials, to include a surface charge, e.g., a positive or negative charge, and/or to alter the polarity or hydrophilicity of the surface) by chemical reaction including, for example, wet or dry oxidation, by coating or depositing a polymer on the surface, or by a grafting reaction. Modifications include, e.g., irradiation, a polar or charged monomer, coating and/or curing the surface with a charged polymer, and carrying out chemical modification to attach functional groups on the surface. Grafting reactions may be activated by exposure to an energy source such as gas plasma, heat, a Van der Graff generator, ultraviolet light, electron beam, or to various other forms of radiation, or by surface etching or deposition using a plasma treatment. In some embodiments, the element(s) can be modified as described in, for example, the U.S. patents listed above.

Typically, the filter 50 has a pore structure, e.g., a pore size (for example, as evidenced by bubble point, or by K_L as described in, for example, U.S. Patent No. 4,340,479), a pore rating, or a pore diameter (e.g., when characterized using the modified OSU F2 test as described in, for example, U.S. Patent No. 4,925,572), that reduces the passage therethrough of white and/or red blood cells. For example, the filter can have a pore diameter of about 10 micrometers (μm) or less. In one embodiment, the filter has a pore diameter in the range of from about 8 micrometers to about 5 micrometers. In another embodiment, the filter and/or at least one filter element 5 has a pore diameter about 5 micrometers or less. In another embodiment, the filter and/or at least one filter element has a pore diameter of about 3 micrometers, or less.

The filter can include a plurality of filter elements having different pore structures and/or at least one element can have a varied pore structure.

In some embodiments of the invention, the filter and/or at least one filter element has a voids volume of about 75% or more, or about 80% or more, e.g., in the range of 85% to about 96%. In one embodiment, at least one filter element has a voids volume of at least about 90%.

In some embodiments wherein the filter includes at least one filter element comprising a fibrous medium, e.g., a polymeric non-woven medium, including some embodiments wherein the biological fluid comprises blood or a blood component, the filter has a nominal effective fiber surface area of at least about .2 M^2. In another illustrative embodiment, the filter has a nominal effective fiber surface area of at least about .3 M^2, and can have a nominal effective fiber surface area of at least about .35 M^2.

In accordance with some embodiments of the invention, wherein the filter comprises at least one filter element comprising a fibrous medium, the filter and/or the at least one filter element has a density of about 4000 g/ft^3 (about 0.14 g/cm^3) or less (in some embodiments about 3800 g/ft^3 (about 0.13 g/cm^3) or less), wherein the density is calculated according to the following equation, at a given average fiber diameter and voids volume:

$$\text{Density (g/ft}^3\text{)} = \frac{\text{basis weight of the fiber (g/ft}^2\text{) X number of layers in the filter element X (12 inches/1 ft)}}{\text{thickness of the element (inches).}}$$

For example, a fibrous filter element according to some embodiments of the invention has a density in the range of from about 2550 g/ft^3 to about 4000 g/ft^3 (about 0.09 to about 0.14 g/cm^3). In other illustrative embodiments, a fibrous filter element has a density in the range of from about 2550 g/ft^3 to about 3200 g/ft^3 (about 0.09 to about 0.11 g/cm^3), or a density in the range of from about 3220 g/ft^3 to about 4000 g/ft^3 (about 0.11 to about 0.14 g/cm^3).

Typically, the filter removes at least some level of the white blood cells (and possibly other biological fluid components) by sieving. In some embodiments, the filter also removes at least some level of white blood cells (and possibly other biological fluid components such as platelets) by adsorption.

In a typical embodiment, the filter reduces the level of platelets and white blood cells in the biological fluid passing therethrough by a factor of at least about 1 log for each component, preferably, at least about 2 logs. In some embodiments, the filter reduces the level of platelets by a level of at least one log (e.g., reducing the level from about 1 x 10^9/mL to about 1 x 10^8/mL), and reduces the level of white blood cells by a

level of at least three logs.

Without being limited to any particular mechanism, it is believed the reduction or elimination of other components of the biological fluid as the fluid passes through the filter reduces the potential for "noise" (particularly background noise) in the analysis chamber. Since the background noise is reduced, the markers or indicators of microbe metabolism (such as, for example, pO_2 and glucose) can be more accurately detected.

For example, in those embodiments wherein oxygen (e.g., pO_2) is detected in the analysis chamber, the reduced level of platelets present minimizes the change in the level of pO_2 that could be attributed to the metabolism of the platelets. In other words, since pO_2 can be consumed by platelets and microbes such as bacteria, the reduced presence of the non-microbe components improves the capability of detecting "microbe consumed" pO_2.

In another illustration, in those embodiments wherein lactate and/or glucose is detected in the analysis chamber, the reduced level of white blood cells and red blood cells present minimizes the change in the level of lactate and/or glucose that could be attributed to the metabolism of these components. Since glucose can be consumed by red and white blood cells and microbes such as bacteria, and lactate can be formed as the blood cells and microbes metabolize, the reduced presence of the non-microbe components improves the capability of detecting "microbe consumed" glucose and/or "microbe formed" lactate.

Typically, using the illustrated embodiments for reference, the microbes are detected in the analysis chamber 20. However, if desired, the filtered fluid, or a portion thereof, can be transferred from at least one chamber or container to another, e.g., passed to at least one additional chamber, container or device (not shown), before detection of the microbes. Accordingly, the analysis chamber can comprise the additional chamber(s), container(s), or device(s). For example, the filtered fluid can be passed to an additional container, and at least a portion of the filtered fluid can be passed to one or more analysis chambers for analysis. Alternatively, or additionally, at least a portion of the filtered fluid can be passed to an additional container for analysis. If desired, the additional chamber(s) or container(s) can have different configurations and/or be made

from different material(s) than that of analysis chamber 20. Illustratively, the analysis chamber 20 can have a "bag-like" configuration and be made from a plasticized flexible material, and the additional chamber can have a "tube-like" configuration and be made from, for example, glass or plastic. The chamber 20 and the additional container(s) can also differ with respect to, for example, the reagent(s) contained therein.

Alternatively, or additionally, in some embodiments (not shown), the filter device includes the analysis chamber, and the microbes are detected therein. For example, in one embodiment wherein the filter comprises a filter device, e.g., comprising a filter housing having an inlet and an outlet and defining a fluid flow path between the inlet and the outlet, with the filter element disposed across the fluid flow path, the "downstream" portion of the filter includes the analysis chamber (e.g., a portion of the downstream section of the housing can allow the filtered sample to be separated and/or isolated from the filter element) where microbes can be detected.

In accordance with the invention, microbes can be detected directly (e.g., using reagents that bind to the microbe), or, more preferably, indirectly (e.g., by detecting indicators and/or markers of the microbes' metabolism, e.g., nutrients consumed by the microbes, metabolic products and/or byproducts produced by the microbes). Illustrative indicators and/or markers include at least one of ATP, pH, glucose, lactate and lactic acid (e.g., as reflected by changes in pH), pO_2 and pCO_2. In some preferred embodiments, the detected indicators and/or markers include at least one of pO_2 and pCO_2.

The indicators and/or markers can be detected in liquid and/or in gas. For example, a probe can be placed in an analysis chamber wherein the chamber is partially filled with liquid containing microorganisms, and the probe can be placed in the liquid, or in the gas or "head space" above the liquid. Accordingly, microorganisms can be detected upon detecting the indicators and/or markers in the liquid or in the gas above the liquid. In some embodiments, the liquid and/or gas can be withdrawn from the chamber and analyzed elsewhere, e.g., in an additional chamber, container, or device. In accordance with some embodiments of the invention, e.g., wherein microorganism metabolism is monitored over time, the withdrawn liquid and/or gas can be returned to

the analysis chamber after each analysis. If desired, particularly for those embodiments wherein gas is withdrawn and it is desired to maintain the initial volume of gas in the chamber, the returned gas can be supplemented, e.g., with a controlled volume of sterile air.

A variety of equipment, devices and/or protocols are suitable for detecting microbes. Illustratively, one or more probes, sensors, instruments, reagents and/or reagent strips can be utilized, e.g., placed in or on the analysis chamber 20. In some embodiments, the devices, e.g., probes and/or sensors, are self-contained and suitable for one-time use. Embodiments of systems according to the invention can include these items pre-assembled and/or pre-attached, e.g., before biological fluid is passed into the container 10 and/or analysis chamber 20. Alternatively, or additionally, one or more of these items can be assembled and/or attached during or after the passage of fluid into container 10 or analysis chamber 20.

In a variation of the embodiment illustrated in Figure 1, conduit 2 can include a sheathed connector (e.g., a needle) or a dockable portion, allowing subsequent connection to analysis chamber 20 when desired. Such configurations are especially suitable for those embodiments wherein different sterilization protocols are utilized for different elements of the system.

Suitable equipment and devices include, but are not limited to, at least one of probe devices (e.g., gas probes); gas chromatographs; blood gas analyzers; head space analyzers, including head space analyzers for oxygen, carbon dioxide, and combined oxygen/carbon dioxide analyzers (such as, for example, the CHECKMATE® system, Topac Inc., Hingham, MA); biosensors, e.g., enzymatic systems, including enzymatic systems wherein the measured voltage reflects the presence and/or level of the indicator(s) present; membrane interfaces; reagent (e.g., dye) detection systems (including fluorescent reagent detection systems, particularly for detecting fluorescent compounds that are quenched in the presence of oxygen); the BioProbe® Luminometer (Pall Corporation), e.g., for detecting ATP; as well as the BACTEC™ MGIT™ 960 System (Becton Dickinson Microbiology Systems, Sparks, Maryland), e.g., utilizing fluorescent compounds sensitive to the presence of oxygen.

Typically, using the exemplary multiple bag set 1000 illustrated in Figure 3 for reference, the containers 10-13, and the conduits 1, 2, and 60-66, are made from commercially available materials used in biological fluid (e.g., blood) processing systems. More typically, they are made from plasticized materials, e.g., plasticized polyvinyl chloride (PVC). Exemplary plasticized PVC materials include, but are not limited to, PVC plasticized with dioctylphthalate (DOP), diethylhelxylphthalate (DEHP), or trioctyltrimelliate (TOTM), e.g., triethylhexyl trimellitate.

In some embodiments, the analysis chamber 20 (sometimes referred to below as the detection chamber) is made from the same materials as the containers and conduits. In other embodiments, the chamber can be made from a different material, e.g., glass, or a thermoplastic material (for example, as used for the housing for filter device 55).

In accordance with the invention, including some embodiments wherein pO_2 and/or pCO_2 is detected in the analysis chamber, at least a portion of the analysis chamber, for example, at least about 50% of the surface area of at least one side wall of the chamber, is capable of allowing gas transmission therethrough. However, in other embodiments, the chamber can be substantially impermeable to gas.

If desired, the analysis chamber 20 can be substantially flexible, e.g., it can collapse or deform when the reservoir is empty and is unsupported by external means. For example, the chamber 20 shown in Figures 1-3 can be substantially flexible.

Alternatively, the analysis chamber 20 can have sufficient rigidity that it does not collapse or deform when the reservoir is empty and is unsupported by external means.

In some embodiments, at least a portion of the analysis chamber 20, (e.g., a side and/or bottom wall) is resilient. For example, the side walls of the chamber 20 as shown in the Figures can be resilient, and the chamber can have sufficient rigidity that it does not collapse when empty. As used herein, the term "resilient" refers to the property of springing back, e.g., to regain, either fully, or approximately, an original position or shape after having been deformed, e.g., bent, stretched, or compressed. Illustratively, at least one wall (or a portion thereof) "springs back" to its previous position or shape after compression. Typically, during use, the process of the wall springing back to its previous position creates a negative differential pressure in the chamber, and this causes

fluid to enter the chamber.

In yet another embodiment, the analysis chamber 20 comprises an evacuated container, e.g., a stoppered tube. For example, in a variation of the embodiment illustrated in Figure 1, the conduit 2 includes a sheathed connector such as a needle that can be unsheathed and used to puncture the stopper of the tube. Since the tube can be evacuated before use, the negative pressure can cause fluid to be passed from the container 10 and through the filter 50 into the chamber 20.

The containers 10-13, as well as the analysis chamber 20, can be of any suitable size and shape, and can include other structure, e.g., any suitable number of ports, transfer leg closures, connectors and/or attached conduits.

Typically, the analysis chamber 20 is suitable for containing at least about 2 ml, more typically at least about 3 ml of biological fluid, e.g., in the range of from about 5 ml to about 50 ml, or more. In some embodiments, containers 10-13 are commercially available flexible blood bags.

The system can include at least one connector, and typically includes a plurality of connectors. In the embodiment illustrated in Figure 3, the system 1000 includes at least one connector 40, that has at least three branches, e.g., the connectors can be in the form of Y- or T-connectors. Suitable connectors are known in the art.

The system can include one or more flow control devices such as a clamp, seal, valve, transfer leg closure, or the like. Typically, the system includes a plurality of flow control devices, and they can be located within or on the conduits and/or the containers. For example, the Figures illustrate embodiments having a flow control device 25 associated with conduit 1. Typically, using the illustrative set illustrated in Figure 3 for reference, flow control devices are associated with one or more of the conduits interposed between containers 10-13.

Embodiments of the system can include additional elements such as at least one of a vent (including a gas inlet and/or a gas outlet), and a gas collection and displacement loop. Additionally, or alternatively, the system can include, for example, one or more additional conduits, containers, and/or connectors.

As noted above, in a typical embodiment the filter device 55 comprises a housing

and a filter 50 comprising a filter element 5. Illustratively, the filter device comprises at least one inlet and at least one outlet, and defining a fluid flow path between the inlet and the outlet, and at least one filter comprising a filter element across the fluid flow path. Any housing of suitable shape to provide an inlet and an outlet may be employed. In those embodiments having a rigid housing, the housing may be fabricated from any suitably rigid, impervious material, including any impervious thermoplastic material, which is compatible with the fluid being processed. In an embodiment, the housing is fabricated by injection molding from a polymer, more preferably a transparent or translucent polymer, such as an acrylic, polypropylene, polystyrene, or a polycarbonate resin. Not only is such a housing easily and economically fabricated, but also it allows observation of the passage of the liquid through the housing.

The housing may include an arrangement of one or more channels, grooves, conduits, passages, ribs, or the like, which may be serpentine, parallel, curved, circular, or a variety of other configurations.

Preferably, the filter 50 (e.g., the filter device 55) is sterilizable, as is the sampling arrangement 100. Systems according to the invention (including systems further comprising the analysis and/or detection equipment such as probes and/or sensors) are preferably closed systems. A variety of suitable sterilization protocols are known in the art.

The present invention is suitable for use with a variety of biological fluids, and a plurality of processing arrangements can be included in a system or set. For example, a multiple blood bag set can include multiple processing arrangements, e.g., for detecting microorganisms in a plurality of separated blood components, blood products and/or in reagents utilized during the processing of blood components and products. Illustratively, processing arrangements can be placed in fluid communication with containers for containing packed red cells, platelet-rich-plasma, platelet concentrate and/or plasma, and portions of each of these fluids can be passed into the processing arrangement(s) to allow microbes to be detected.

In some embodiments, microbes can be detected at a concentration of about 10^6 (or less) colony forming units (CFU)/mL in the portion of biological fluid in the analysis

chamber. Illustratively, microbes can be detected at a concentration in the range of about 10^3 to about 10^7 CFU/mL of fluid in the chamber. In one embodiment of the invention, microbes can be detected at a concentration of at least about 10^5 CFU/mL of fluid.

In some embodiments, the system (for example, the analysis or detection chamber) can include at least one reagent, solution, additive, growth medium and/or culture medium, e.g., to prevent a lag in growth of the microbes and/or to improve the growth rate. In some embodiments, minimizing the lag in growth and/or improving the growth rate allows the microbes to be detected more quickly. A variety of reagents, solutions, additives, growth media and/or culture media are suitable. These additional materials can be in dry form (e.g., a powder or a "tablet") or liquid form. If desired, e.g., wherein the materials are in dry form, for example, tablet form, further components, ingredients and/or additives, that can be inert materials such as at least one of maltose and mannitol, can be included, e.g., to provide bulk. In one embodiment, the analysis chamber includes sodium polyanethol sulfonate (SPS) in dry or liquid form. As noted above, additional materials can be included in the chamber with the SPS.

Alternatively, or additionally, some components, ingredients and/or additives can provide for interacting with, neutralizing and/or inhibiting other components, ingredients, additives, products and/or byproducts present in and/or produced in the analysis chamber. Illustratively, in an embodiment wherein the presence of citrate, or the presence of a high level of citrate in the analysis chamber is undesirable, embodiments of the invention include providing calcium, e.g., to inhibit and/or neutralize the citrate. In some embodiments of the invention, a complement activation inhibitor is provided in the analysis chamber.

In one embodiment of a method according to the invention, and using the exemplary system illustrated in Figure 3 for reference, a unit of blood is obtained from a source such as a donor, and passed along conduit 64 into container 11 (such as collection bag, that typically includes anticoagulant). Typically, the blood is centrifuged, to form a sediment layer comprising red blood cells and a supernatant layer comprising platelet-rich-plasma (or to form a sediment layer comprising red blood cells, an

intermediate buffy coat layer, and a supernatant layer comprising platelet-poor-plasma).

If desired, one or more layers can be passed through a filter device, such as a leukocyte depletion filter device. For example, packed red blood cells can be passed from container 11 along conduit 65 and through leukocyte depletion filter device 201 and conduit 66 into container 13. Additionally, (typically before the red blood cells are passed from container 11) platelet-rich-plasma (PRP) can be passed from container 11 along conduit 63 and through leukocyte depletion filter device 200, conduit 62, connector 40 and conduit 60 into container 10 of system 500.

Subsequently, the PRP (typically leukocyte-reduced PRP) is centrifuged, and plasma can be passed from container 10 into container 12 via conduit 60, connector 40, and conduit 61, leaving platelet concentrate in container 10.

If desired, two or more units of platelet concentrate can be combined (e.g., pooled) in a container (e.g., container 10 as shown in Figures 1 and 2) before passing a portion of platelet concentrate into the processing arrangement.

A portion of the platelet concentrate (e.g., single donor apheresis platelets or pooled platelets) is passed into the processing arrangement 100, such that fluid passes along conduit 25 and through the filter element 5 of filter 50. The filtered fluid, that may contain microbes such as bacteria, passes into analysis chamber 20. The filter depletes the fluid of biological fluid components by reducing the level of components such as at least one of platelets, white blood cells and red blood cells, thus reducing the potential for noise in the analysis chamber.

In a preferred embodiment, microbes, if present, are detected in the analysis chamber 20. If desired, the microbes can be allowed to grow in the chamber 20 (e.g., for about 8 hours or more, in some embodiments, for at least about 24 hours or more) before detection. Alternatively, or additionally, the presence of microbes can be monitored continuously or intermittently over time, and, if desired, a plurality of analysis chambers can be utilized.

If desired, particularly in some of those embodiments wherein the analysis chamber is detached from the source container, e.g., the source container is no longer in fluid communication with the analysis chamber, and a tether allows the source container

to be associated with the analysis chamber, the source container can be processed differently than the analysis chamber. For example, after a conduit (e.g., conduit 1 and/or 2 in Figures 1 and 2) interposed between the source container and analysis chamber is sealed and cut, the analysis chamber can be processed in conditions more conducive to rapid microorganism growth (e.g., stored at a higher than ambient temperature, e.g., a temperature of about 35-37° C), and the source container can be processed in a more conventional manner (e.g., stored at an ambient temperature of about 22° C).

Microbes can be detected (directly or indirectly) using a variety of indicators, markers, equipment, devices and/or protocols as described earlier. In some embodiments, microbes can be detected without adding a microbe growth medium to the biological fluid.

If desired, embodiments of the invention can include automated tracking and/or automated detection protocols and equipment. For example, one or more containers and analysis chambers can include indicia (e.g., bar coding labels) with information such as the source(s) of the biological fluid, blood type, additive(s) utilized, an indication whether a level of indicator and/or marker (e.g., pO_2 or CO_2) was reached, and this information can be tracked, combined with the detection results, and provided in whatever format is suitable, e.g., indicated (in machine readable form if desired) on at least one of the analysis chamber and the storage container and/or as a print-out.

EXAMPLE 1

Two units of leukocyte-reduced platelet-rich-plasma (each unit is approximately 250 ml) are obtained, and each unit is separated into 50 ml portions that are placed in individual plastic satellite bags, wherein the bags are suitable for storing platelets.

Two groups of filter devices are provided, as described in more detail below. One group of filter devices is used to filter "spiked" platelet-rich-plasma, and the other group is used as a control, i.e., to filter "non-spiked" platelet-rich-plasma.

Two groups of systems according to an embodiment of the invention are provided wherein, for each system, the bag suitable for storing platelets is placed in fluid

communication with an analysis chamber via flexible plastic tubing, with a filter device interposed between the bag and the chamber, as generally shown in Figure 1. The analysis chamber includes a port (as shown in Figure 1), and the system also includes an adapter for use with a pO_2 probe. The adapter is a length of tubing including a duckbill-type check valve.

The two groups of systems are essentially identical.

Each filter device includes a 25 mm diameter housing having an inlet and an outlet defining a fluid flow path between the inlet and the outlet with a filter across the fluid flow path. The filter, that has a face area of .849 in^2 (.000542 m^2) and a nominal effective fiber surface area of .399 m^2, is a filter element made from 10 layers of melt-blown polybutylene terephthalate fibers. Each layer, comprising fibers having an average fiber diameter of about 3 micrometers, has a voids volume of 92% and a thickness of 0.020 inches. The filter element is gas plasma treated as disclosed in International Publication No. WO 93/04763.

The analysis chamber in each system is a 3 cm x 5 cm pouch manufactured from PVC film plasticized with diethylhelxylphthalate (DEHP), wherein the walls of the pouch are permeable to gas. The plasticized PVC film, having a wall thickness of 0.015 inches, has an oxygen transfer rate of 5 micromoles per hour for a bag having a surface area of 350 cm^2 (corresponding to an ASTM oxygen transfer rate of about 470 $mL/m^2/day$).

Five of the 50 ml portions of platelet-rich-plasma (PRP) are inoculated with Escherichia coli obtained from the American Type Culture Collection (ATCC) at a suspension level to provide a target inoculum of about 1 CFU/mL. The other five portions of PRP are not inoculated.

About 24 hours after preparing the portions of PRP, about 5 mL of fluid from each container is passed from the container, through a filter device, into the analysis chamber, and the clamp between the filter device and the container is closed. After an additional 24 hours, a fiber optic oxygen sensor (Ocean Optics, Inc.), is inserted into the adapter connected to each analysis chamber and operated according to the manufacturer's instructions.

The pO_2 in each analysis chamber containing unspiked fluid has reached an equilibrium oxygen tension level of at least 100 mm Hg. The pO_2 is each chamber containing inoculated fluid is reduced to a level well below 100 mm Hg.

This example shows that systems according to an embodiment of the invention provide for the passage of plasma and a level of E. coli through a filter, and allow the E. coli to be detected.

EXAMPLE 2

Multiple units of leukocyte-reduced platelet concentrate (PC) from human donors are obtained. Each unit of PC is prepared in a closed system from a unit of whole blood, and is stored overnight (on a platelet shaker) in a commercially available platelet storage bag. As will be described in more detail below, 4 units of PC are placed into various groups (each group contains 4 individual units to be processed and analyzed) to provide "spiked/filtered" and "unspiked/filtered" units.

The "spiked" units are spiked with either gram positive or gram negative bacteria. The bacteria are: Staphylococcus aureus (gram positive), Klebsiella pneumoniae (gram negative), Enterobacter cloacae (gram negative), and Group B streptococcus (gram positive). Each unit in a given group is spiked with a single type of bacteria at a level of 200-500 cfu/ml and filtered shortly after spiking.

For each group, an equal number of unspiked/filtered units are studied in parallel, as negative controls.

Each filter device includes 25 mm diameter housing, and a filter comprising a single fibrous filter element having a face area of .000542 m^2, a nominal effective fiber surface area of .399 m^2, and 10 layers of melt-blown polybutylene terephthalate fibers. The basis weight of the fibers is 5.2 g/ft^2. Each layer, including fibers having an average fiber diameter of about 3 micrometers, has a voids volume of 92% and a thickness of 0.020 inches. The filter element is surface modified as disclosed in U.S. Patent No. 4,925,572. The filter has a critical wetting surface tension of about 66 dynes/cm. The filter has a pore diameter of 8 micrometers as determined by the modified OSU F-2 test as generally described in U.S. Patent No. 4,925,572.

The density of the filter element, wherein the density is calculated as [the basis weight of the fibers (5.2 g/ft^2) x the number of layers (10) x (12 inches/1 ft)]/the thickness of the filter (0.2 inches) = 3120 g/ft^3 (= 0.110 g/cm^3).

The platelet storage bag is sterile-docked to a filter device leading to a sterile flexible pouch. As will be explained in more detail below, a first sample of the PC is passed through the filter into the pouch. Subsequently, a first portion of the first sample is passed from the first pouch into a tube containing a fluorescent indicator, and a second portion of the first sample is passed from the first pouch into another tube containing the fluorescent indicator, wherein the tube also contains media (broth).

After the first filter device/flexible pouch is disconnected from the platelet storage bag, a second filter device/flexible pouch is sterile-docked to the bag. The second flexible pouch has sodium polyanethol sulfonate (SPS), therein. A second sample is filtered, and passed into the second pouch. The concentration of the SPS in the second sample is 0.05%. First and second portions of the second sample (each portion containing filtered fluid and SPS) are passed from the second pouch into separate tubes containing fluorescent indicators, one tube with media, and one tube without media.

Unspiked PC is also filtered to provide first and second samples, and the samples are divided into portions and passed into separate tubes in the same manner as described above.

Accordingly, for each unit of PC, a total of four different Indicator Tubes are utilized for the samples: Media/SPS, Media/no SPS, no Media/SPS, no Media/no SPS.

The tubes are commercially available BBL™ MGIT™ Mycobacteria Growth Indicator Tubes (Becton Dickinson) including a fluorescent indicator containing ruthenium chloride petahydrate. One set of Indicator Tubes also includes media, i.e., a broth base conventionally used for mycobacteria growth, the other set lacks the broth.

The fluorescent indicator in each Indicator Tube is sensitive to the presence of oxygen, and as bacteria in the sample consume the oxygen, the fluorescence is detected. The fluorescence is monitored using a BACTEC™ MGIT™ 960 System (Becton Dickinson).

On the average, at least about 25% of each type of bacteria passes through the

filter, with the exception of B streptococci, wherein about 12% passes through. The level of platelets and white blood cells in the filtered samples is below the detection limit.

The spiked/filtered samples show a change in fluorescence. The unspiked/filtered samples show essentially no change in fluorescence.

On the average, the bacteria in the spiked samples are positively detected in less than 24 hours in both sets of tubes. However, the Klebsiella pneumoniae in the Indicator Tube without SPS is positively detected in about 50 hours.

This example shows bacteria are detected if platelets and white blood cells, that are metabolically active, are removed.

EXAMPLE 3

Three units of leukocyte-reduced platelet concentrate (PC) are obtained. Each unit of PC, that is approximately 55 ml, is prepared in a closed system from a unit of whole blood, and is stored overnight in a commercially available platelet storage bag.

Three units of PC are spiked with E. coli, at 100-500 cfu/ml.

The filter device is as described in Example 2. The system is arranged as generally shown in Figure 2, and the analysis chamber 20 is a 3 cm x 5 cm pouch manufactured from PVC film plasticized with diethylhelxylphthalate (DEHP), wherein the walls of the pouch are permeable to gas. The plasticized PVC film, having a wall thickness of 0.015 inches, has an oxygen transfer rate of 5 micromoles per hour for a bag having a surface area of 350 cm^2 (corresponding to an ASTM oxygen transfer rate of about 470 $mL/m^2/day$).

Four 6 ml filter samples are taken from each unit of PC, wherein a new filter device and analysis chamber is sterile docked to the PC bag for each filtration. Two of the four analysis chambers for the samples from a unit of PC contain a detergent, sodium polyanethol sulfonate (SPS), to provide a concentration of .05% SPS in the sample.

The concentration of the platelets in the PC is about 1.3×10^9 platelets/ml. The concentration of the platelet in the filtered samples is about 1.1×10^7 platelets/ml.

The platelet bags and pouches are stored on a platelet shaker for 24 hours at 22°

C. Portions of each sample are passed into a blood gas analyzer (model Stat Profile 3, Nova Biomedical) that is operated in accordance with the manufacturer's instructions to determine the PO_2.

Each of the spiked samples exhibits PO_2 levels well below 100 mm/Hg. The samples including SPS exhibit PO_2 levels well below 100 mm/Hg in less than 24 hours. The samples without SPS exhibit PO_2 levels well below 100 mm/Hg in 30 to 48 hours.

This example shows that systems according to an embodiment of the invention provide for the passage of plasma and a level of E. coli through a filter, while depleting the platelet concentration by about 2 logs, and allow the E. coli to be detected.

EXAMPLE 4

Units of leukocyte-reduced platelet concentrate are obtained, spiked with E.coli at 100-500 cfu, and samples are passed from platelet storage bags through filter devices into flexible pouches (analysis chambers) having SPS therein as generally described in Example 3. Analysis of the influents and effluents shows the concentrations of the platelets are decreased by about 2 logs upon passing through the filter devices.

At 0, 24, 30 and 48 hours, samples are taken from the platelet storage bags and analysis chambers to determine the bacteria counts, and the oxygen concentration is determined in the storage bags and analysis chambers using a head space analyzer for oxygen (CHECKMATE® oxygen analyzer, Topac, Inc.).

At 24 hours, the pO_2 concentrations in the storage bags are well below 100 mm/Hg, and the pO_2 concentrations in the analysis chambers are above 100 mm/Hg. The bacteria counts in the bags and chambers show little growth has occurred.

At 30 hours, the pO_2 concentrations in the storage bags and the analysis chambers are well below 100 mm/Hg. The bacteria counts in the bags and chambers show the bacteria counts have increased by several logs.

This example shows systems according to embodiments of the invention improve the capability of detecting bacteria-consumed pO_2 by reducing the presence of platelets (that also consume pO_2).

All of the references cited herein, including publications, patents, and patent applications, are hereby incorporated in their entireties by reference.

While the invention has been described in some detail by way of illustration and example, it should be understood that the invention is susceptible to various modifications and alternative forms, and is not restricted to the specific embodiments set forth. It should be understood that these specific embodiments are not intended to limit the invention but, on the contrary, the intention is to cover all modifications, equivalents, and alternatives falling within the spirit and scope of the invention.

WHAT IS CLAIMED IS:

1. A biological fluid processing system comprising:

a first container suitable for holding a biological fluid, the container having an internal volume for receiving the biological fluid; and

a processing arrangement comprising a biological fluid analysis chamber, suitable for receiving a plasma-containing portion of biological fluid passed from the internal volume of the container, and a filter interposed between, and in fluid communication with, the first container and the biological fluid analysis chamber, the filter comprising at least one filter element comprising at least one porous medium;

wherein the filter allows the passage of microbes and plasma from the first container to the analysis chamber, and reduces the passage of platelets from the first container to the analysis chamber.

2. A microbe detection system comprising:

a first flexible container suitable for holding a biological fluid possibly containing microbes, the container having an internal volume for receiving the biological fluid;

a microbe detection chamber, suitable for receiving a microbe-containing portion of the biological fluid passed from the internal volume of the first flexible container;

a filter comprising a filter element comprising at least one porous medium, interposed between, and in fluid communication with, the first flexible container and the detection chamber, the filter allowing a portion of the microbes in the biological fluid to pass from the first flexible container into the detection chamber;

wherein the detection system is arranged to allow microbes in the biological fluid passing through the filter to be detected.

3. The system of claim 1 or 2, wherein the filter reduces the passage of white blood cells and platelets from the first container to the chamber.

4. The system of claim 3, wherein the filter depletes the white blood cell concentration/mL by a factor of at least about 2 logs, and depletes the platelet

concentration/mL by a factor of at least about 1 log.

5. The system of claim 4, wherein the filter is adapted to provide a filtered fluid having a platelet concentration of less than about 4×10^8 platelets/ml in the chamber.

6. The system of any preceding claim, wherein the filter element comprises at least one porous fibrous medium.

7. The system of claim 6, wherein the filter element has a density in the range of from about 0.09 g/cm^3 to about 0.14 g/cm^3 (about 2550 g/ft^3 to about 4000 g/ft^3).

8. The system of any preceding claim, wherein the filter has a pore diameter of less than 8 micrometers.

9. The system of any preceding claim, arranged to allow an indicator of microbe metabolism to be detected in the chamber.

10. The system of claim 9, wherein the indicator is consumed by microbes and non-microbes in the biological fluid, and the system is arranged to reduce the level of the indicator consumed by non-microbes in the chamber as compared to the level of the indicator consumed by the microbes in the chamber.

11. The system of any preceding claim, arranged to detect pO_2 in the chamber.

12. The system of any preceding claim, arranged to detect pCO_2 in the chamber.

13. The system of any preceding claim, being capable of detecting microbes at a concentration of at least about 10^5 colony forming units (CFU)/mL of the microbe- and plasma-containing biological fluid.

14. The system of any preceding claim, comprising a closed system.

15. The system of any preceding claim, wherein the chamber is detachable.

16. The system of claim 15, wherein the microbes can be detected after the chamber is detached.

17. The system of any preceding claim, wherein the filter and the chamber are integrally attached.

18. The system of any preceding claim, wherein the filter, the chamber, and the container are integrally attached.

19. The system of any preceding claim, arranged to allow the microbes to be more concentrated per unit volume of fluid in the chamber than in the first container.

20. The system of any preceding claim, arranged to allow the level of microbes in the chamber to increase for at least about 24 hours before detection.

21. The system of any preceding claim, arranged to allow the level of at least one indicator of microbe metabolism in the chamber to decrease for at least about 24 hours before detection.

22. The system of any preceding claim, wherein the chamber has a volume of about 10 ml or less.

23. The system of any preceding claim, wherein at least a portion of the chamber allow gas transmission therethrough.

24. The system of any preceding claim, including at least a second container interposed

between the filter and the chamber.

25. The system of any preceding claim, wherein the filter has a critical wetting surface tension (CWST) of at least about 0.58 erg/mm^2 (about 58 dynes/cm).

26. A biological fluid processing system comprising:

a flexible container suitable for holding a biological fluid, the container having an internal volume for receiving the biological fluid;

a biological fluid analysis chamber, suitable for receiving a plasma-containing portion of biological fluid passed from the internal volume of the flexible container, wherein the analysis chamber is arranged to allow the bacterial contamination of the plasma-containing portion to be determined;

a filter interposed between, and in fluid communication with, the flexible container and the biological fluid analysis chamber, the filter comprising a filter element including a porous medium;

wherein the filter element allows the passage of plasma and bacteria from the flexible container to the analysis chamber, and reduces the passage of leukocytes from the flexible container to the analysis chamber.

27. A biological fluid analysis device comprising:

a filter comprising a filter element that allows the passage of plasma- and bacteria-containing biological fluid therethrough, while reducing the passage of blood cells therethrough;

a biological fluid analysis chamber downstream of the filter, wherein the chamber is disposed to receive the fluid passing through the filter, and all fluid passing into the chamber first passes through the filter, the chamber comprising a flexible container.

28. A method for processing a biological fluid comprising passing a portion of the biological fluid through the filter of any preceding claim, and determining whether microbes are present in the chamber.

29. A method for detecting microbes in a biological fluid comprising:

obtaining a biological fluid in a first container;

passing a portion of the fluid from the first container into an analysis chamber, wherein passing the fluid from the container into the chamber includes passing the fluid through a filter adapted to allow microbes to pass therethrough, the filter comprising at least one porous medium; and

determining whether microbes are present in the chamber.

30. The method of claim 29, including passing plasma- and bacteria-containing biological fluid through the filter.

31. The method of claim 29 or 30, wherein passing the fluid through the filter includes depleting white blood cells from the fluid.

32. The method of any of claims 29-31, wherein passing the fluid through the filter includes depleting platelets from the fluid.

33. The method of any of claims 29-32, wherein passing the fluid through the filter includes depleting red blood cells from the fluid.

34. A method for processing a platelet-containing biological fluid comprising:

obtaining a platelet- and plasma-containing biological fluid in a first container;

passing a portion of the fluid from the first container into a processing arrangement comprising a filter including at least one filter element including at least one porous medium, wherein the filter allows the passage of microbe- and plasma-containing fluid therethrough and reduces the passage of platelets therethrough, the processing arrangement also including an analysis chamber downstream of the filter element;

receiving a filtered plasma-containing fluid in the analysis chamber; and

determining whether microbes are present in the filtered plasma-containing fluid.

35. The method of claim 34, wherein the platelet- and plasma-containing biological fluid in the first container comprises platelet concentrate.

36. The method of claim 35, wherein the filtered plasma-containing fluid in the analysis chamber comprises platelet- and white blood cell-depleted fluid.

37. The method of any preceding claim, including detecting the level of pO_2 in the analysis chamber.

38. A biological fluid processing system comprising:

a first container suitable for holding a biological fluid, the container having an internal volume for receiving the biological fluid; and

a filter in fluid communication with the first container, the filter comprising at least one filter element including at least one porous medium, the filter including a biological fluid analysis chamber, suitable for receiving a plasma-containing portion of biological fluid passed from the internal volume of the container;

wherein the filter allows the passage of microbes and plasma from the first container to the analysis chamber, and reduces the passage of platelets from the first container to the analysis chamber.

39. A method for detecting microbes in a biological fluid comprising:

obtaining a biological fluid in a first container;

passing a portion of the fluid from the first container into a microbe analysis chamber, wherein passing the fluid from the container into the chamber includes passing the fluid through a filter capable of allowing the passage of microbes therethrough, the filter comprising at least one porous medium; and

determining whether microbes are present in the biological fluid passed through the filter.

40. The method of any of claims 30, 31, and 34-37, wherein passing the fluid through the filter includes reducing the platelet concentration/mL by a factor of at least about 1 log.

41. The method of claim 40, wherein the filtered fluid has a platelet concentration of less than about 4×10^8 platelets/mL.

42. The method of claim 41, wherein the filtered fluid has a platelet concentration of about 4×10^7 platelets/mL or less.

43. The method of any of claims 30, 31, 34-37, and 40-42, wherein passing the fluid through the filter includes reducing the white blood cell concentration/mL by a factor of at least about 1 log.

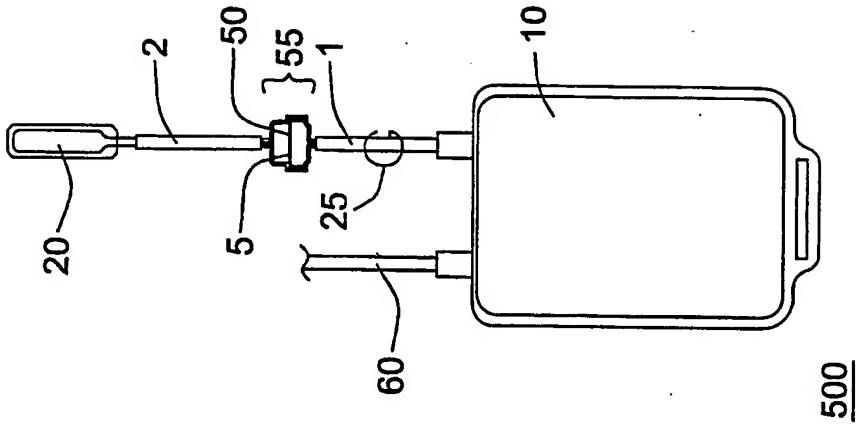

FIG. 2

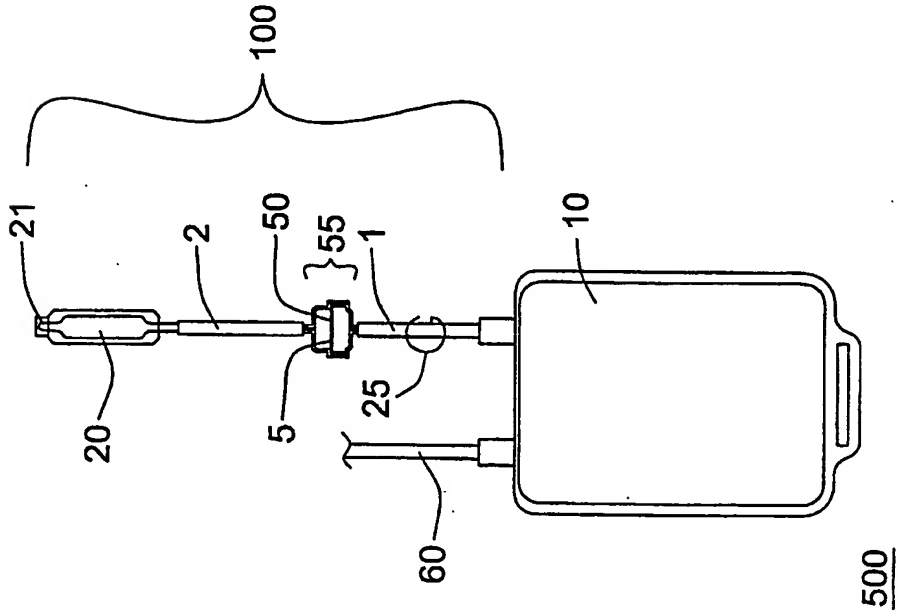

FIG. 1

FIG. 3